IRREGULAR GOUT: HUMORAL FANTASY OR SATURNINE MALADY*

RICHARD P. WEDEEN, M.D.
Veterans Administration Medical Center
East Orange, New Jersey

IRREGULAR gout is one of those concepts, universally held in the past, that has slowly receded into oblivion. There was a time when virtually all diseases came under this heading. Although irregular gout is no longer part of the physician's vocabulary, I shall present some evidence that consignment of this term to arbitrary abstractions of the past may be unjustified. The idea of irregular gout may not have been simply a consequence of conceptual fantasies derived from humoral doctrine, but rather the literal description of frequent, albeit unrecognized, encounters with lead-induced gout.

To trade the history of lead poisoning and gout it is essential to understand the evolution of diagnostic criteria by which physicians have defined these diseases at different periods. Colic followed by the palsy was the signature of lead intoxication recognized in the 17th century.[1] In prescientific medicine, symptomatic plumbism was most often identified in the setting of obvious exposure, that is, among lead workers or in epidemics of colic induced by lead-contaminated wine. Lead acetate was widely used as an internal and external therapeutic agent so that iatrogenic lead poisoning was also commonplace but rarely recognized. In the Paracelsan tradition, heavy metals were used in the treatment of virtually all diseases, sometimes including gout.[2] Excessive lead absorption could not be identified in the absence of the classical symptoms.

More recently, the diagnosis of lead toxicity has been confirmed by assessment of lead inhibition of hemoglobin synthesis and by measurement of blood lead concentrations. But hematologic abnormalities are seen only with relatively severe acute intoxication. Chronic, low dose lead absorption in the remote past may produce neither symptoms nor changes

*Presented at a meeting of the Section on Historical Medicine of the New York Academy of Medicine November 17, 1983.

This research was supported by the Medical Research Service of the Veterans Administration.

in blood, yet be sufficient to cause late sequelae. Unsuspected lead absorption in quantities too small to induce colic or wrist drop may nevertheless result in excessive accumulation in bones. Bone lead is presently assessed using the EDTA lead mobilization test.[3] $CaNa_2EDTA$ combines with lead in bone and soft tissues and the lead chelate is excreted in the urine. Using this test, the presence of excessive body lead stores can be established even when the source of exposure is unrecognized by the victim. Detection of unrecognized lead poisoning using the EDTA test thus represents a recent (and still controversial) step in the evolution of diagnostic criteria for lead poisoning.[4]

A similar evolution of the medical concept of gout has occurred over the past century. Today, gout is rather narrowly defined as an acute arthritic affliction sometimes complicated by kidney disease or hypertension. This change in conceptualization of the disease has been attributed to the passing of humoral doctrine.[5] Humoral theory could, indeed, accommodate an impressive array of natural and supernatural phenomena. Although medical understanding of disease is always constrained by concepts of causation, traditional medicine was further restricted by self-imposed adherence to received dogma.

According to Francis Adams' 1849 translation of the Hippocratic corpus, the Father of Medicine considered gout a disease of mature males; eunuchs and premenopausal women were spared.[6] Adams noted that Galen had expanded these views, ascribing the affliction to "debauchery, intemperance and an hereditary taint." What is less often recalled is that Hippocrates also considered some forms of gout incurable. "With regard to persons affected with the gout," he contended, "those who are aged, have tofi in their joints, who have led a hard life, and whose bowels are constipated, are beyond the power of medicine to cure." Galen too, observed that gout had a tendency to migrate to the stomach.[7]

We have here all the themes that surrounded medical descriptions of gout for 2,000 years. Gout was not simply arthritis of the great toe, *podagra;* rather it was a systemic illness, the consequence of debauchery and intemperance. Of particular interest, gout was consistently associated with abdominal complaints. Gout of the stomach was illustrated along with gout of the foot in the caricatures by George Cruikshank. Cruikshank not only depicted King George IV by prominently displaying his gouty toe, but indicated also the associated pain in the stomach (Figure 1). The dry gripes were part of the dissipated king's afflictions

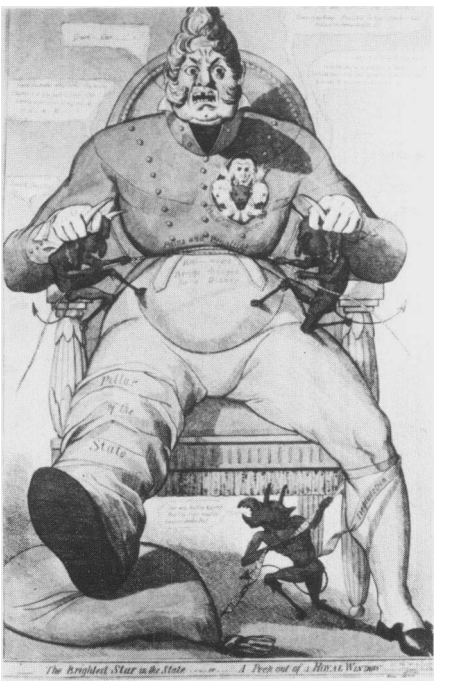

Fig. 1. "The Brightest Star in the State," drawn by George Cruikshank in 1820, depicts King George IV suffering from "pains and penalties" of the stomach as well as podagra. From the collection of William Helfand.

(Figure 2). Indeed, the royal malady, interpreted by some as hereditary porphyria,[8] might in fact have been due to lead, which could also explain the royal gout.[9] Constipation and colic, the most common symptoms of irregular gout, may provide clues to the origin of classical views of gout.

The physiology of Hippocrates and Galen was grounded in humoral theory. The natural, vital, and animal spirits depended on a balance between the four humors; blood, phlegm, black bile, and yellow bile. Subtle analysis of these abstract "fluids" was used to account for the wide variation of physiologic functions in health and disease. Phlegm, it was believed, was a watery substance generated in the pituitary, which imparted to the body cold and moist qualities. These were the qualities ascribed both to colic and to the gout.

Lazarus Riverius, professor at the University of Montpelier in the 17th century and follower of the great French Renaissance physician Jean Fernel, expanded medieval views of this ancient philosophy. Phlegm, he

Fig. 2. In "The Privy Council" gouty George IV shares his abdominal "gripes" with his counselors as depicted by George Cruikshank in 1816. British Museum No. 1816-12757.

claimed, because of its coldness induced acidity and by putrefaction became salt. When heated, these salts become "gypseous flegme" and when "indurated into a Tophaceous matter, almost resembling lime, this other perplexeth the joints causing the knotty Gout."[10] Riverius further explained that "incrassated" or "vitrious flegme" is gathered in the intestines and doth not seldome torture them with painful fits of Collick."

The malleable idea of phlegm thus encompassed both gout and the colic and, by ingenious reasoning, could include virtually all the ills that flesh is heir to. The concept of the humors provided a satisfying, if metaphorical, explanation of the appearance of tophi as well as of podagra. The word "gout" is derived from the Latin verb *gutta,* meaning "to run into" or "to drop." By analogy, the dispersal of phlegm from the pituitary to the extremities evolved into the concept of a peccant or morbific matter and finally into ill defined saline particles which dropped into the great toe. Eventually identified in blood by Garrod as uric acid,[11] for many centuries the circulating cause of gout was considered to be a far more potent and abstract substance. Until the present century, dispersal of this morbific matter through the body was consid-

ered more calamitous than its localization in the joints. The nonarticular manifestations of gout were seen as the inevitable consequences of the failure of the morbific matter to express itself as acute podagra.

Innumerable symptoms of nonarticular gout were classified under the broad heading "irregular gout." The variety of modifiers used was as vast as the conditions they described. These included retrocedent, misplaced, atonic, visceral, anomalous, atopic, alternating, asthenic, larval, masked, latent, repelled, nervous, wandering, premature, and imperfect gout, to cite a few of the most commonly used terms. The proliferation of adjectives was inversely proportional to the useful information they conveyed. With motivation generated by self-evident truth, their proponents were moved to passionate defense of vague classification.

In the midst of these semantic debates, several distinct symptom complexes consistently recurred. "Irregular" gout attacked primarily the stomach, the nervous system, and the kidneys. Sydenham claimed that the translation of gout to the stomach was often fatal. His less renowned contemporary, William Atkins,[12] reported further that "some have it not in the joints at all, but in the inward parts only; and usually when it is in the inward parts, the pain is exceeding great for a short time, and runneth about like a Cholick." In a commentary on Sydenham's *Treatise of the Gout.* George Wallis[13] noted that "the paroxysms of the disease are commonly preceded by an affection of the stomach: many exciting causes act first upon the stomach: and the atonic and retrocedent gout are most commonly and chiefly affections of the same organ." To the layman "gout of the stomach" was considered a distinct entity and was so classified by the founder of Methodism, John Wesley, in his enormously popular *Primitive Physic,* first published in 1747.[14]

The long and colorful association of gout with alcoholic drinks, now almost forgotten, supports the view that stomach complaints often dominated the gouty diathesis.[15] The three great causes of gout were succinctly stated by Soranus of Ephesus[16] in the second century; "wine, indigestion and venery." The etiologic role of wine is as recurrent in early discussions of gout as were the abdominal symptoms. Gout was universally agreed to be the daughter of Bacchus and Venus.[17]

A composite of the gouty diathesis was provided by James Gillray in the companion caricature to his well known "The Gout," drawn in 1799. "Punch Cures the Gout" illustrates the concomitants of drinking rum punch (Figure 3). The participants at this depressing celebration demonstrate the familiar symptoms of "irregular gout"; podagra, colic

Fig. 3. "Punch Cures the Gout," drawn by James Gillray in 1799, illustrates the consequences expected from lead-laden rum; gout, colic and cachexia. The New York Public Library.

and cachexia, an accurate description of the long term effects of lead-laden rum.

But rum punch was by no means the only source of "poison in the pot." William Heberden,[18] for example, included pains of the stomach, palsies, and cerebral symptoms in his descriptions of "irregular gout." He particularly suspected Portuguese wines as the cause of the colic, but never connected lead in wine with the appearance of gout.

In the 18th century Dr. Oliver of Bath used port wine for aversion therapy of the gout.[19] To get his patients to renounce the Portuguese imports, Oliver had them drink port, followed immediately by ipecac. After a few weeks of retching, his patients never imbided Portuguese wine again. Garrod[20] also suspected Iberian wines. "My own experience of the relative power of alcoholic liquors in inducing gout is this," he stated, "that the wine ordinarily drank in this country, as port and sherry, and other strong varieties are the most potent in their operation."

What was there about port that gave it the peculiar propensity to produce the gout? In 1897 a gouty free-lance reporter ventured an explana-

tion.[21] "What renders Port especially harmful," wrote George Ellwanger in his *Meditations on the Gout,* "is the adventitious alcohol... and other foreign ingredients.... The undue proportion of Gout that has long existed in England as compared with other countries, can be traced largely to the Revolution of 1688." Following the Treaty of Methuen in 1703, he explained, import duties on wine from Portugal were greatly reduced, and Englishmen switched to Portuguese wines to assuage their thirst. "the greatest quantity ever exported from Portugal was in 1825," Ellwanger continued, "when 40,277 tons, equivalent to forty thousand cases of gout, were shipped to England." Ellanger noted that one of the most dangerous adulterants in Portuguese wine was lead.

This hypothesis was verified by Gene V. Ball in 1971. In several samples of aged port preserved for English connoisseurs, Ball found extraordinarily high concentrations of lead.[22] Lead in alcoholic drinks may well have contributed to the gouty diathesis of the past.

The history of lead poisoning is at least as long as that of gout. The hypothesis that the fall of Rome was accelerated by the practice of sweetening and preserving wines with lead acetate was proposed by Gilfillan in 1965, and is supported by numerous culinary references that have survived from ancient times.[23] Gilfillan noted that as women became liberated during the later stages of the Roman Empire, they shared in the lead-laced wines previously reserved for their patrician husbands.[24] In addition, they regularly whitened their skin using lead oxide powder. The resulting infertility led to Roman laws hastily implemented to encourage fecundity and thus to overcome the deleterious effects of lead on reproductive function. At the same time, gout first appeared in Roman women. "The nature of women has not altered but their manner of living," observed Seneca,[25] "for while they rival men in every licentiousness, they equal them too in their bodily disorders. Why need we then to be surprised at seeing so many of the female sex affected with gout?" Seneca did not, however, discern the saturnine component of the gout of Roman ladies.

The discovery of saturnine gout should probably be credited to Johann Jacob Wepfer.[26] In 1671, writing of the "paresis after colic from wine," Wepfer attributed colic, neurologic symptoms, gout, and nephritis to the practice of adding lead acetate to wine. Wepfer used "rectified oil of vitriol" (sulfuric acid) to prove the presence of lead in wine, but his demonstration attracted little attention outside Germany. Using chemical techniques, Wepfer showed that colic and gout had the same origin.

This was again demonstrated in 1778 by James Hardy, who noted that leaded cider was not only the cause of the Devonshire Colic, as had been so elegantly shown by George Baker, but that lead was also responsible for the gout long prevalent in Devonshire, His pamphlets of 1778 and 1780[27] in defense of Baker's thesis recorded this idea in their titles. Hardy's polemics, however, seem to have obscured the content of his remarks.

Substantial support for the existence of saturnine gout was provided by Sir Alfred Baring Garrod. In his classic monograph on gout published in 1859, Garrod pointed out that at least one quarter of his gout patients were lead workers who, at one time or another, had sustained symptomatic lead poisoning.[28] He later increased this estimate to one third.[29] It seems likely that even more of the "irregular gout" encountered by Garrod was saturnine in origin than even he suspected, a consequence of industrial exposure, lead-contaminated water supplies, and the English predilection for Portuguese wine. Garrod demonstrated that lead acetate (an accepted therapeutic agent in his time) decreased urinary excretion of uric acid, thus providing the biochemical basis for saturnine gout. More recent evidence suggests that lead both increases uric acid production and diminishes its excretion, thus further promoting the hyperuricemia conducive to gout.[30] Garrod also recognized kidney disease as a common cause of death among gout patients.

Modern physicians have reassigned most manifestations of "irregular gout" to other categories of disease. Lead colic is currently considered a distinct entity, but saturnine gout remains the subject of controversy. Of the myriad disorders once contained under the rubric "retrocedent gout," only kidney disease remains. But even this last relic of "irregular gout" shows signs of slipping away from the uric acid diathesis. Histologically, the gouty kidney, first described by de Castelnau in 1843,[31] was very similar to the lead nephropathy described by Lancereaux 20 years later.[32] Indeed, Lancereaux's patient was an artist who habitually held his paint brushes in his mouth. He suffered from gout, but encephalopathy caused his death. His kidneys showed inerstitial nephritis at autopsy, a histopathologic finding currently considered to arise from a variety of causes, including lead, gout, and hypertension. During the 19th century such renal disease was usually attributed to alcohol. More recently, this histologic pattern sometimes has been misconstrued as "pyelonephritis."

Colic, palsy, and podagra were recognized as distinct entities by the

earliest physicians because of their dramatic symptoms combined with the fact that the victims survived long enough to tell their tales. The introduction of chemical methods into medicine by Johann Jacob Wepfer, George Baker, and Alfred Baring Garrod increased both sensitivity and specificity for detecting these syndromes. In modern times, measurement of blood lead and heme synthesis defects improved the diagnosis of excessive acute exposure to lead. The ability to measure body lead stores by the EDTA lead mobilization test has further increased precision for detecting lead poisoning. By use of the chelation test, saturnine gout can be diagnosed even in the absence of colic, palsy, renal failure, or an unequivocal history of exposure to lead.[33] Using the EDTA mobilization test, we have found that the contribution of lead to the renal disease of gout and "essential" hypertension is frequently overlooked in contemporary patients.[34] Much of the interstitial nephritis attributed to gout during the past two centuries may have been the result of unrecognized lead poisoning. The diagnosis of saturnine gout was missed because of inadequate diagnostic criteria. The belief that hyperuricemia of the usual degree encountered in gout patients is detrimental to kidney function is challenged by these observations.

Identification of lead as a contributing cause of renal failure in gout patients is of more than academic interest. Unlike "essential" hypertension or gout, lead nephropathy is both preventable and sometimes reversible.[35] Hyperuricemia is universal in renal failure, but gout is extremely rare, except when the kidney disease is saturnine in origin. The association of gout with lead nephropathy has been clearly demonstrated among moonshine whiskey consumers in the southeastern United States where illicit brews are often heavily contaminated with lead. Alcohol again appears to be the link between gout, "irregular gout," and the noxious effects of lead.

In conclusion, I suggest that considerable evidence from past and contemporary accounts indicates that irregular gout was not a fantasy derived from humoral doctrine but had a sound basis in observation. From the initial appearance of gout with colic in Rome to the epidemics in Devonshire and the moonshine belt in the United States, lead in alcoholic drinks may have accounted for the prominent nonarticular symptoms associated with the gouty diathesis. The belief that wine caused gout and colic may not have been simply an error born of prescientific medical theory. The more recent association of both gout and lead with hypertension and renal failure may, similarly, be well founded in observation. Fi-

nally, the highly variable incidence of renal failure reported in patients with hyperuricemia or gout may be accounted for by the variability of unsuspected lead poisoning in the past as well as the present. The lessons of the past have not been systematically rejected, but seem to have been overlooked. Unsuspected lead toxicity, lacking the classical symptoms, may still be commonplace in modern society. The etiology of the delayed complications of excessive lead absorption, gout, hypertension, and renal disease still often go unrecognized.

REFERENCES

1. Stockhausen, S.: *Traite des mauvais effets, de la fumee de la litharge (1649).* Paris, Ruault, 1776, pp. 13-20.
2. Baker, G.: An attempt towards an historical account of that species of spasmodic colic, distinguished by the name of colic of Poitou. *Med. Trans. Lond. 1:* 319-63, 1768.
3. Emmerson, B. T.: Chronic lead nephropathy. *Kidney Int. 4:* 1-5, 1973.
4. Wedeen, R. P.: *Poison in the Pot: The Legacy of Lead.* Carbondale, Ill., Southern Illinois University Press. In press.
5. Jarcho, S.: Some lost, obsolete, or discontinued diseases: Serous apoplexy, incubus, and retrocedent ailments. *Trans. Stud. Cell Phys. 2:* 241-66, 1980.
6. Adams, F.: *The Genuine Works of Hippocrates.* London; Sydenham Society, 1849, pp. 756,57.
7. Ibid, p. 261.
8. Macalpine, I. and Hunter, R.: The "insanity" of George III: A classic case of porphyria, *Br. Med. J. 1:* 65-71, 1966.
9. Wedeen, op. cit.
10. Riverius, L.: *The Universal Body of Physick in Five Books: Comprehending the several Treatises of Nature, of Diseases and their Causes, of Symptomes, of the Preservation of Health and of Cures.* London, Eversden, 1657, p. 32.
11. Garrod, A. B.: Second communication on the blood and effused fluids in gout, rheumatism and Bright's disease. *Med. Chir. Trans. Lond. 37:* 49-61, 1854.
12. Atkins, W.: *A Discourse Shewing the Nature of the Gout.* London, Fabian, 1694, p. 6.
13. Sydenham, T.: *The Works of Thomas Sydenham, M.D. on Acute and Chronic Diseases,* Wallis, G. translator. London, Robinson, 1788, p. 18.
14. Wesley, J.: *Primitive Physic: or, an Easy and Natural Method for Curing most Diseases.* 16th ed. London, Hawes, 1774, p. 85.
15. Nriagu, J. O.: Saturnine gout among Roman aristocrats. *N. Engl. J. Med. 308:* 660-63, 1983.
16. *Caelinus Aurelianus,* Drabkin, I. E., translator. Chicago, University Press, 1950, 929-31.
17. Wedeen, R. P.: Punch Cures the Gout. *J. Med. Soc. N.J. 78:* 201-06, 1981.
18. Heberden, W.: *Commentaries on the History and Cure of Diseases (1802).* York, Hafner, 1962, p. 388.
19. Grant, W.: *Some Observations on the Origin, Progress and Method of Treating the Atrabilious Temperament and Gout.* London, Cadell, 1779, p. 31.
20. Garrod, A. B.: *A Treatise on Gout and Rheumatic Gout.* London, Longmans, Green, 1876, p. 221.
21. Ellwanger, G. H.: *Meditations on Gout with a Consideration of its Cure Through the Use of Wine.* Cambridge, University Press, 1897, pp. 134-35.
22. Ball, G. V.: Two epidemics of gout. *Bull. Hist. Med. 45:* 401-08, 1971.
23. Nriagu, J. O.: *Lead and Lead Poisoning in Antiquity.* New York, Wiley,

1983, pp. 331-38.
24. Gilfillan, S. C.: Lead poisoning and the fall of Rome. *J. Occup. Med. 7:*—53-60, 1965.
25. Graham, W. and Graham, K. M.: Our gouty past. *Can. Med. Assoc. J. 73:* 485-93, 1955.
26. Wepfer, J. J.: Paresis post colicum ex vino. In: *Micellanea Curiosa, sive Ephemeridum Medico-Physicarum Germanicarum Curiosarum, Annus Secundus, Anni scilicet DCLXXI.* Frankfurt, 1688, pp. 70-1.
27. Wedeen, Punch Cures the Gout.
28. Garrod, A. B.: *The Nature and Treatment of Gout and Rheumatic Gout.* London, Walton Maberly, 1859, p. 237.
29. Garrod, A. B.: Clinical remarks on a case of lead-poisoning. *Lancet 2:* 781-82, 1870.
30. Wedeen, *Poison in the Pot.* In press.
31. de Castelnau, H.: Observations et reflexions sur la goutte et le rhumatisme, et specialement sur quelques accidents graves qui peuvent se manifester dans le cours de ces deux affections. *Arch. Gen. Med. Par. 3:* 285-314, 1843.
32. Lancereaux, E.: Note relative a un cas de paralysie saturnine avec alteration des cordons nerveux et des muscles paralyses. *Gaz. Med. Paris 17:* 709-13, 1862.
33. Batuman, V., Maesaka, J. K., Haddad, B., et al.: The role of lead in gout nephropathy. *N. Engl. J. Med. 304:* 520-23, 1981.
34. Batuman, V., Landy, E., Maesaka, J. K., and Wedeen, R. P.: The contribution of lead to hypertension with renal failure. *N. Engl. J. Med. 309:* 17-21, 1983.
35. Wedeen, *Poison in the Pot.* In press.